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KRAMER LEVIN NAFTALIS & FRANKEL LLP
INTELLECTUAL PROPERTY DEPARTMENT
919 THIRD AVENUE
NEW YORK, NY 10022

| EXAMINER | |
|---|---|
| SAIDHA, TEKCHAND | |
| ART UNIT | PAPER NUMBER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

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*Below is a communication from the EXAMINER in charge of this application*

*COMMISSIONER OF PATENTS AND TRADEMARKS*

## ADVISORY ACTION

☒ THE PERIOD FOR RESPONSE:

a) ☐ is extended to run ___ ___ or continues to run ✓ from the date of the final rejection

b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 7/11/03 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE. _____

2. ☒ Newly proposed or amended claims 30-35 & 37-38 would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing an appeal, the proposed amendment ☑ will be entered ☐ will not be entered and the status of the claims will be as follows:

   Claims allowed: 30-35 & 37-38
   Claims objected to: _____
   Claims rejected: 13-29

   However;

   ☐ Applicant's response has overcome the following rejection(s): _____

4 ☐ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because _____

5 ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficient reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☐ Other

***Advisory Action***

1. Applicants' after-final amendment filed on 7.11.03 (Paper No. 29), is acknowledged.

2. Claims 13-35 & 37-38 are pending.

3. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

4. Applicants arguments have been considered and further in view of amendment to claims 30-35 and 37-38, which now recite or reference chimeric β-lactamase into the claims, claims 30-35 and 37-38 are allowed.

5. ***35 U.S.C. § 112, first paragraph***

Claims 13-29 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a method of determining the amount of an analyte in a test sample using a chimeric β-lactamase as the starting enzyme, and comprising selected amino acids sequence insert in the loop of the rim of the active site residues 103-105, for example; or the alpha. 11 helix residues 271-272 of the R-Tem β-lactamase, for example; in order that the enzyme be defined as a chimeric enzyme, which are then selected for binding by antibodies psa10 and psa66. The claims are directed to a method of determining the presence of an analyte using any (a) chimeric enzyme as the starting enzyme, wherein said chimeric enzyme is constructed by inserting a sequence of said mimetope (binding site moiety) into a sequence of said starting enzyme by replacing at least <u>one amino acid</u> of the starting enzyme with a sequence of said mimetope. However, the guidance provided for a single site specific chimeric β-lactamase is inadequate for one skilled in the art to

develop a method using any chimeric enzyme construct for determining the presence or amount of an analyte in a test sample. Factors to be considered in determining whether undue experimentation is required, are summarized in *re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) [ *Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, © the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim. The factors most relevant to this rejection are the scope of the claims, unpredictability in the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

The claims are directed to a method for determining the presence of an analyte in a test sample using any enzyme as the starting enzyme, modifying the enzyme(s) to create a functional or enzymatically active chimeric enzyme having a binding site moiety, to which a binding molecule can attach. From the guidelines provided for construction of chimeric β-lactamase and the skill of the artisan in the area of molecular biological and enzymology it would have been possible to modify the mimetope as evidenced by SEQ ID Nos. 1-78 which is inserted by replacing at least a single amino acid in the chimeric β-lactamase structure from any source in order to selectively modulate the catalytic activity of the β-lactamase upon binding. Selective insertion sites have been identified, for example, the loop preceding the alpha -11 helix (residues 271-272 of β-lactamase. However, the transfer of such a construct to any enzyme from any source in order to first produce a chimeric

enzyme and further attempt to selectively insert mimetopes pertinent to any enzyme in order to create a chimeric enzyme which can successfully attach itself to a binding molecules, lacks adequate guidance, is unpredictable and would result in undue experimentation. It lacks adequate guidance because the chimeric insertion developed for β-lactamase by insertion of the specific mimetopes to achieve binding in β-lactamase may not necessarily function with any enzyme and such a binding function for determining the presence or amount of an analyte in a test sample is neither exemplified nor is a matter of routine experimentation. This is because the modification of mimetope amino acid(s) and its insertion into any enzyme, including those not characterized yet will not necessarily result in producing an active chimeric enzyme in every other enzyme because every other enzyme is distinct in its sequence, regions of active site or susceptibility to modifications, leading to highly unpredictable results. Thus, the specification fails to provide guidance to other enzymes, other than β-lactamase and at the specific positions, that can be successfully utilized in effectively creating chimeric enzymes and the appropriate steps required for such constructs. Every enzyme being distinct , it remains unpredictable that the instant disclosure on β-lactamase be sufficient to develop a method for determining analytes using other any chimeric enzyme or any sequence insert (Clam 13) , which can successfully attach itself to any binding molecules (claims 14-19), or where the analyte and substrate contact the enzyme simultaneously or in steps (claims 20-25), or where the test sample contains the analyte (claim 25) or where the mimetopes is any one of the sequences of SEQ ID NOS : 1-78 (claims 26-27) or where the enzyme activity of the chimeric enzyme is in the unbound state (claims 28-29). Therefore, the skilled artisan would require guidance, such as the (a)

the sequence of the β-lactamase (SEQ ID NO: ) or the other chimeric enzymes (by SEQ ID Nos:) and guidance to where the sequence inserts of the mimetope (BSM), identification of the active catalytic and binding sites and the effect(s) of such modifications on the functionality of the different enzymes constructs, in order to make and use chimeric enzymes in a manner commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

6. Applicants Arguments (previous):

It must be emphasized that the above rejection is under 35 U.S.C. § 112, first paragraph (enablement) and is not a written description rejection.

Applicants have failed to address the key issues of the rejection. On page 19, for example, the Applicants incorporate a portion of a paragraph from the previous Office Action, which is out of context. It is unclear what evidence the Applicants are looking for from the examiner. Please point to the lines of the Office Action the Applicants are referring to, as it not clear what the basis of Applicants' following conclusion is :

"However, the Examiner appears to be assuming his own conclusion: he has presumed that there is substantial variation in the sequence among various species of β-lactamase.....The Examiner has not provided any evidence to support this conclusion".

Sequence homology or conservation of sequence homology is relied upon in order to evaluate how certain amino acid changes would effect or alter the enzyme activity. In the instant case, for example, if an amino acid change is made in the structure of a specific β-lactamase at a specific

position to obtain a chimeric β-lactamase, the same change and effect may be difficult to reproduce in another species of β-lactamase with a different structure, and even more difficult to obtain in another enzyme or protein or starting molecules, such as a transferase, an oxido-reductase, subtilisin, alkaline phosphatase, etc., having an entirely different structure or sequence. While it is known that many amino acid substitutions or replacement are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, catalysis and in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions. However, applicants have provided little or no guidance beyond the mere presentation of specific sequence inserts in β-lactamase to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in any enzyme (or protein) which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Such a definition might also read on previously characterized proteins, or alternatively, might include proteins with additional functions or activities neither envisioned nor enabled by applicants in the current invention. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) with regard to the issue raised above.

Applicants further argue that the Examiner maintains, without any evidence to support his conclusion, that β-lactamase includes a diverse number of enzymes, presumably having dissimilar sequence homologies and functionalities.

In response, Applicants submission of the MINI-REVIEW (Bush et al. Antimicrobial Agents and Chemotherapy, 1995, 1211-1233), describes and supports the Examiner's point of view that there are diverse classes (A-D) of β-lactamases including Cephalosporins, Penicillin & β-lactams with differing sequence similarities. Figure 1, shows a dendrogram, describing the various β-lactamase and their structural relationships. Vertical branch lengths extending to the left are inversely proportional to the similarity between sequences.

Therefore a modification made in one type of the β-lactamase having a specific sequence may not necessarily translate to or appropriate to make in another kind of β-lactamase or any other enzyme.

No substantial new arguments were presented nor a clear or specific response to previous arguments filed.

Arguments (previous) :

Applicants (page 5 of the response) argue that working examples while limited to the use of β-lactamase does not provide sufficient basis to reject then present claims. The specification need not provide examples or specific description of every embodiment for the entire scope of the invention. More importantly the specification clearly teaches a skilled artisan to select a starting enzyme and a binding site moiety insertion site (e.g., a mimetope insertion site) at a location

preferably remote from the active site of the enzyme, and that such a selection will preserve the activity of the starting enzyme in the chimeric construct.

In response, the claims do not recite that the binding site moiety insertion site is located remote from the active site. Therefore, there is no basis for such an argument. Applicants have provided no direction that a method exemplifying β-lactamase and the inserted mimetopes (or epitope) of SEQ ID Nos 1-78 can be extended to any type of enzyme(s) and to any mimetope hitherto undescribed and be used in the chimeric construct.

Applicants further argue 'employing the 3-dimensional structure in one of the techniques that is used for selecting and specifically identifying a desired location on the molecule to the engineered (Specification, page 14). Three-dimensional structure of most proteins or enzymes require routine experimentation.

Unfortunately, the level of skilled artisan have not reached the point where by one can elucidate the 3-D structure of enzymes or proteins without undue experimentation. Protein crystallization and determining 3-D structures of proteins by X-ray crystallography is still very much a complicated and an unpredictable art, and therefore the reliance upon such a technique for elucidating the 3-D structure of any protein and extending the teachings of a chimeric β-lactamase to any enzyme without adequate guidance is unreasonable, undue and not enabled.

No substantial new arguments were presented nor a clear or specific response to previous rejections or arguments filed.

7. Claims 13-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13-29 are directed to a method of determining the amount of analyte using any chimeric enzyme or 'the claimed genus' from any organism wherein any of the amino acid residues along the peptide chain is modified to make chimeric enzyme. Claim 24 recite a 'single species' in enzyme beta-lactamase. The specification describes amino acids inserts in the loop of the rim of the active site residues 103-105, for example; or the alpha. 11 helix residues 271-272 of the R-Tem β-lactamase, for example; in order that the enzyme be defined as a chimeric enzyme, which are then selected for binding by antibodies psa10 and psa66. The prior art teaches the R-Tem beta-lactamase amino acid sequence which forms the reference or the base structure of the chimeric β-lactamase. The specification does not describe a representative number of species to the genus. A 'representative number of species' requires that the species which are expressly described be representative of the entire genus. Thus, when there is substantial variation within the genus, it may require a description of the various species which reflect the variation within the genus. In the instant case, however, the description of a single species of the chimeric β-lactamase is not representative of the entire genus which includes any of the other enzyme(s), as the various species reflect variation within the genus. Therefore, if a specific amino acid site is altered in the chimeric β-lactamase, without a clear description of the identities of equivalent site of β-lactamase from other species, such

a alteration or modification may not result in having a similar effect in any genus or species claimed. What constitutes a 'representative number' is an inverse function of the predictability of the art. The number must be sufficient to identify the other members of genus. In an unpredictable art, such as the instant one, wherein a chimeric enzyme is made by insertion of specific mimetopes (SEQ ID NO : 1-78), adequate written description requirement of a genus cannot be achieved by disclosing only one species within the genus. In such a case, where the members of the genus being claimed are expected to vary widely in their identifying characteristics, such as structure or enzyme activity, due to the introduced changes in the mimetope sequence to alter a particular enzyme property, for example, binding, written description for each member within the genus will be necessary. Therefore, the written description requirement is not satisfied.

8. Applicants' Arguments (previous) :

Applicants argue that the claims of the instant invention are not limited of β-lactamases, which is provided exclusively as an example.

In response, it is pointed out that a single β-lactamase is provided as an example, not lactamases from any source. However, in view of the adequate sequence similarity and conservation of the amino acid sequences among the β-lactamase species, a generic claim encompassing any β-lactamase is within the scope of enabling or described disclosure.

Applicants further argue that the invention is to a 'desired target (TM) which can be modified to have at least one binding site moiety (BSM) to which a binding molecule attach (Specification, page 2, lines 10-12). The specification describes the present invention in terms of a generic target

molecule (which may be an enzyme). Pointing to pages 2 & 3 of their specification, Applicants argue that the specification provide 10 examples of what can be used as a target molecule.

A search of Applicants' specification did not reveal 10 examples as argued. Further, Applicants are claiming a method using any chimeric enzyme. Therefore, the rejection is maintained.

No substantial new arguments were presented nor a clear or specific response to previous arguments filed.

9. ***Claim Rejections - 35 U.S.C. § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13 & 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Benito et al. [JBC 271 (25) : 21251-21256 (August 1996), **IDS**]. Benito et al. teach a method for the modulation of enzyme activity (β-Galactosidase) after insertion of a antigenic region of peptide (epitope or mimetope or binding site-moiety) into β-Galactosidase, which is mediated by antibody binding and further point to use of this hybrid or chimeric construct for the rapid detection of specific antibodies in a quick and simple homogenous assay based on the calorimetric determination of β-Galactosidase

activity. All the claim limitations being taught the reference anticipates the method steps written so broadly [see abstract and the entire article, specially results & discussion].

10. Claims 13 & 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan et al. [Protein Engineering 7 (4) : 509-514 (1994), **IDS**]. Brennan et al. teach an epitope (or mimetope) of an HIV protein inserted into bacterial alkaline phosphatase in creating a chimeric enzyme having a mimetope or epitope or binding site-moiety. The enzyme activity of this protein hybrid is modulated upon antibody binding while maintaining phosphatase activity which can be assayed for determining the analyte or substrate in solution. All the claim limitations being taught the reference anticipates the method steps written so broadly [see abstract and the entire article, specially results & discussion].

Applicants argue that amended claims 30 & 34 do not teach chimeric β-lactamase. In response, these claims are no more included in the art rejection. Further, Applicants do not clearly explain how the cited references do not anticipate.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

T. Saidha

Tekchand Saidha
Primary Examiner, Art Unit 1652
July 29, 2003